AACC Better health through laboratory medicine.

PEARLS OF LABORATORY MEDICINE

Pearl Title: **Primary Antibody Deficiencies (PAD)**

Presenter: **Maha N. Syed MD, Joud Hajjar MD, MS**

Affiliation **Baylor College of Medicine**

DOI: 10.15428/CCTC.2018.294439

CCTC Clinical Chemistry Trainee Council

Learning Objective

- Recognize clinical patterns suggestive of Primary Antibody Deficiency (PAD)
- Learn about different presentations of PAD
- Be familiar with the diagnostic methods for PAD.
- Be familiar with common treatments used for PAD.
- Be familiar with complications caused by PAD.

Definition

- Primary antibody deficiency (PAD) syndromes are a group of rare disorders characterized by an inability to produce clinically effective immunoglobulin (Ig) responses.
- Some disorders result from genetic mutations in genes involved in B cell development, whereas others appear to be complex polygenic disorders.

Primary Antibody Deficiencies: Spectrum of disorders

- Selective IgA deficiency
- CVID (Common Variable Immune Deficiency)
- Specific antibody deficiency disorders
- Agammaglobulinemia (Both x-linked and Autosomal recessive)
- Transient hypogammaglobulinemia of infancy
- IgG subclass deficiency
- Selective IgM deficiency
- Hyper IgM syndrome

Selective IgA Deficiency (SIgAD)

- **Prevalence:** 1:400 in the Caucasian population.
- **Definition:** IgA ≤ 7 mg/dl with normal IgG and IgM, normal B-cell numbers, normal specific antibody responses in most patients
- 2/3 of patients are healthy and asymptomatic.
- **Symptoms** include:
  - Autoimmune Disorders: (Idiopathic Thrombocytopenic Purpura, Autoimmune Hemolytic Anemia, Rheumatoid Arthritis, Systemic Lupus Erythematosus , Thyroiditis, and Vitiligo).
  - Sino-pulmonary Infections: (Encapsulated bacteria).
  - Gastrointestinal (GI) Disorders: (Giardiasis, nodular lymphoid hyperplasia, Celiac Disease, and Inflammatory Bowel Disease).
  - Allergic Disease: (Asthma, Allergic Rhinitis, Atopic Dermatitis, and food allergy).

Selective IgA Deficiency Cont'd

- Very rarely, anaphylactic transfusion reactions to plasma-containing blood products, due to presence of small amounts of IgA in blood products which reacts with anti-IgA antibodies present in such patients.
- In rare cases, Selective IgA Deficiency may progress to CVID
- Symptomatic patients should be followed longitudinally to determine if CVID develops.
- **Treatment**: Treat concomitant disorders, prophylactic antibiotics to reduce risk of infection and occasionally a trial of Immunoglobulin Replacement Therapy (IgGRT), if prophylaxis fails.

IgG Subclass Deficiency

- **Definition:** Absent/very low concentration of one or more IgG subclasses, with normal IgA, IgM and total IgG.
- Four different subtypes: IgG1, IgG2, IgG3, and IgG4
- **Symptoms:** Sinopulmonary/GI infections.
- **Diagnosis:** Total serum IgG, IgA, IgM, and IgE. IgG subclasses (obtained at initial evaluation, and only if vaccine response is impaired) Antibody titers to proteins/polysaccharide antigens like diphtheria, tetanus, *Hemophilus influenzae* type b (Hib), and *S. pneumoniae*
- **Treatment:** Prophylactic antibiotics might be considered. IgGRT reserved for patients with abnormal antibody responses and frequent or chronic infections.

Common Variable Immune Deficiency (CVID)

- Most common symptomatic primary immunodeficiency in adults
- **Prevalence**: 1:10,000 - 1: 100,000
- **Etiology:** Impaired B cell differentiation with defective Ig production
- **Symptoms:** Clinically, patients develop recurrent sinopulmonary infections. 20% of patients have non-infectious complications: autoimmunity, chronic lung/GI disease and malignancy.
- **Diagnosis:** Low IgG, IgA and/or IgM AND poor responses to protein and polysaccharide vaccines
- **Treatment**: IgGRT is the standard of care in CVID and has led to decrease in infections and improved survival.

Comparisons in diagnostic criteria of CVID

AACC Better health through laboratory medicine.

	European Society of Immunodeficiency (ESID) 2014	International Consensus Document (ICON) 2016
Similarities	• IgG must be low • IgA or IgM must be low • Other causes of hypogammaglobulinemia ruled out	
Differences	• Patients could have normal vaccine responses, but they should have low memory B cells (<70% of normal age range)	• Impaired vaccine responses must be present
	• Clinical history of increased susceptibility to infections, autoimmunity, granulomatous disorder, unexplained polyclonal proliferation, or positive family history of PAD is required for the diagnosis	• The diagnosis could be established based on laboratory data, without clinical history of infections, autoimmunity, lymphoproliferation or positive family history
	• Diagnosis is established after the age of 4 years	• Onset of symptoms above 2 years of age

Specific antibody deficiency

- **Definition:** Normal IG, normal B-cell numbers, impaired specific antibody responses to polysaccharides vaccines. and *usually*, normal responses to protein based vaccines.
- **Symptoms:** Recurrent sinopulmonary infections.
- **Diagnosis:** IgG, IgG subclasses, IgA, IgM, and IgE. Vaccine response to Tetanus, Diphtheria and PneumoVax®
- **Treatment:** Prophylactic antibiotics, vaccination with conjugated pneumococcal vaccine (Prevnar), IgGRT in severe cases and failure of prophylactic antibiotics.

Polysaccharide vaccine responses

AACC Better health through laboratory medicine.

Vaccine	Phenotype	Response < 6Yr	Response > 6Yr
Pneumococcal conjugate		Normal Response 1.3 mg/mL*	protective antibodies to 70% of the serotypes tested, with at least a 2-fold increase in the titer
	Severe	≤2 protective titers (≥1.3 mcg/mL)	≤2 protective titers (≥1.3 mcg/mL)
	Moderate	<70% of serotypes are protective (≥1.3 mcg/mL)	<50% of serotypes are protective (≥1.3 mcg/mL)
	Mild	Failure to generate protective titers to multiple serotypes or failure of a 2-fold increase in 70 % of serotypes	Failure to generate protective titers to multiple serotypes or failure of a 2-fold increase in 50% of serotypes
	Memory	Loss of response within 6 to 12 months	Loss of response within 6 to 12 months

CCTC Clinical Chemistry Trainee Council

* The consensus value in several studies is 1.3 mg/ml, but a value of 1.6 mg/ml has been used in other studies. *Original table modified for this publication. From: Orange JS, Ballow M, Stiehm ER, et al. Use and interpretation of diagnostic vaccination in primary immunodeficiency: A working group report of the basic and clinical immunology interest section of the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol 2012; 130:S1*

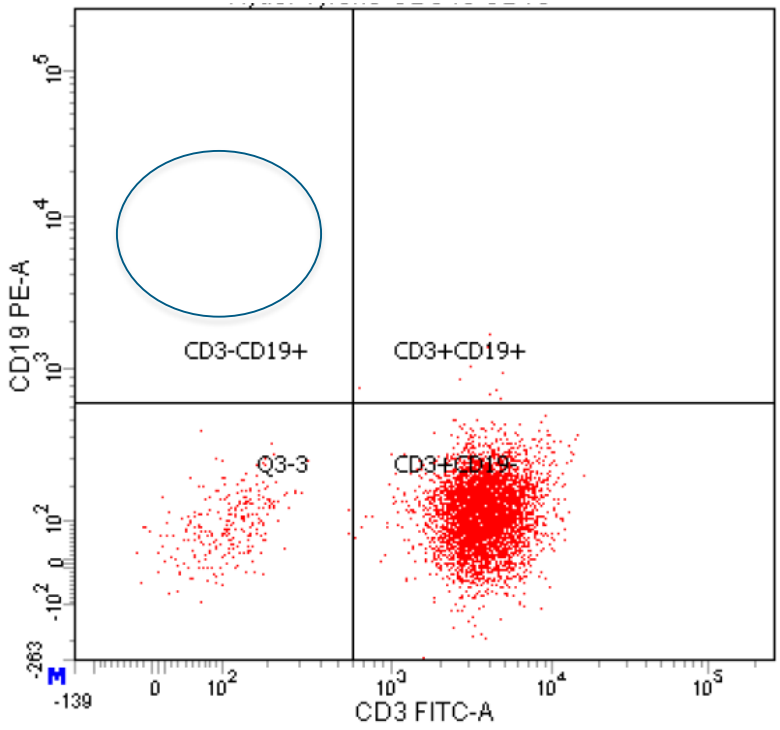
Agammaglobulinemia

- **Prevalence:** 1:379,000 US Live births
- **Etiology:** Failure of B-cells precursors to mature into B-cells, then plasma cells.
- **Genetics:** X-linked in 85-90% of cases, due to a mutation in the BTK* gene, Autosomal recessive in 10-15% of cases due to mutations in IGLL1**, CD79A gene BLNK^{x}, LRRC8°, CD79B gene,PIK3R1 and TCF3*** gene.
- **Symptoms** Upper and lower respiratory tract by:
  - Encapsulated bacteria (*Streptococcus pneumoniae*, *HiB*)
  - *Mycoplasma* and *Ureaplasma* pneumonia, septic arthritis
  - *Pseudomonas* and *Staphylococcus* sepsis particularly in transient neutropenia.
  - Enterovirus infections (*polio, coxsackie, echo virus*), chronic diarrhea, meningitis, and fatal disseminated infection.
- **Diagnosis**: Agammaglobulinemia, deficient antibody responses to immunizations and absent/markedly reduced B cells in peripheral blood (CD19, CD20)
- **Treatment:** Lifetime IgGRT is indicated for all patients.

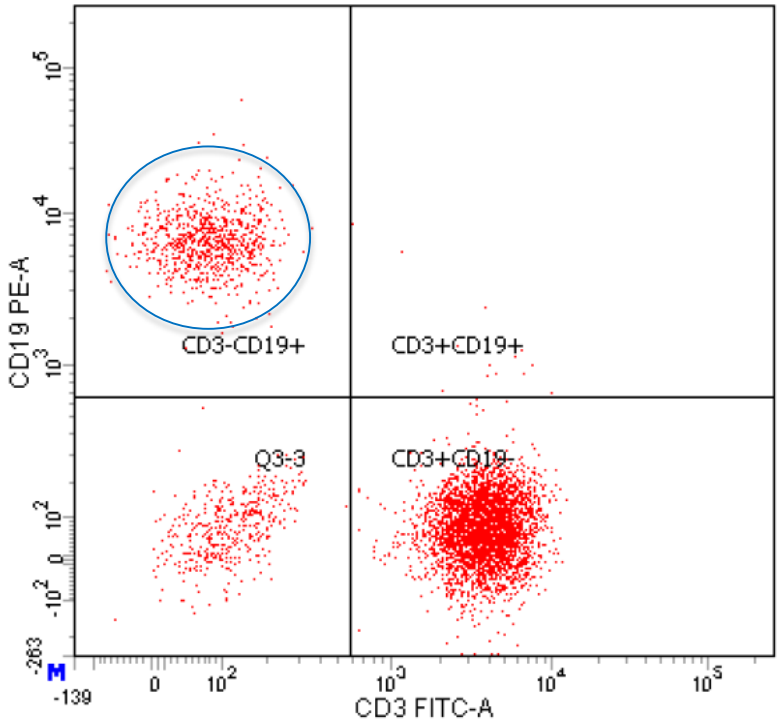
* BTK: bruton tyrosine kinase; **IGLL: immunoglobulin lambda like polypeptide; ˣBLNK: b-cell linker; ˚LRRC8: Leucine-rich repeat-containing protein 8; ^PIK3R1; phosphoinositide-3-kinase regulatory subunit 1; ***TCF3:transcription factor 3;

B cells phenotyping in X-Linked Agammaglobulinemia

Patient



Control



Courtesy of Dr. Sara Nandiwada PhD, Clinical Immunology Laboratory, Texas Children's Hospital, Houston,Texas,USA

Transient Hypogammaglobulinemia of Infancy

- **Etiology:** IgG is transferred through placenta from mother, and wears off in 3-6 months. Occasionally, infant's immune system is not mature → transient hypogammaglobulinemia.
- No inherent defects of B-cell or defects of specific antibody responses
- **Symptoms:** Recurrent sinopulmonary or GI infections, candidiasis and sometimes meningitis.
- **Laboratory:** Low IgG, variably low IgA and rarely low IgM, normal specific antibody responses in most patients, normal B-cell numbers
- **Treatment:** Patients with frequent and/or more severe infections are treated with antibiotic prophylaxis or IgGRT till Ig normalizes.

Hyper-IgM syndrome

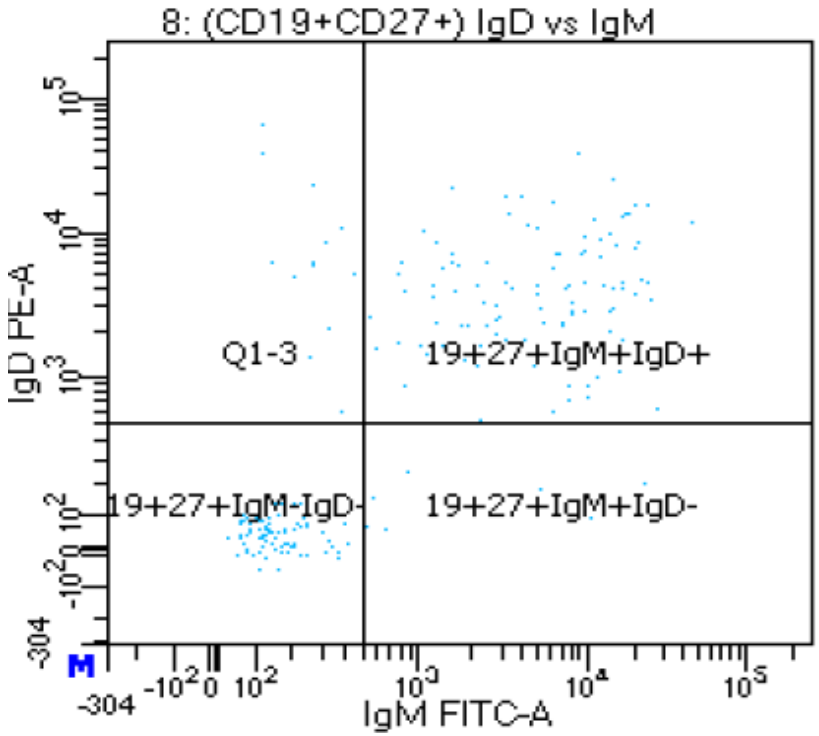
- **Prevalence:** 1:100,000
- **Genetics:** X-linked (CD40L), or autosomal recessive (CD40, UNG*, AID^)
- **Etiology:** Defects in Class-switch recombination (CSR) of Ig, with or without defects of somatic hypermutation (SHM)
- **CD40 /CD40L Deficiency:** is a combined immunodeficiency because of T cell involvement, severe infections, such as *P jirovecii* pneumonia, severe CMV disease and mucocutaneous candidiasis.
- **Complications:** failure to thrive in infants and liver disease (cirrhosis and cholangiocarcinoma)

Hyper IgM syndrome Cont'd

- **Laboratory**: Low IgG, IgA, and IgE with either normal or elevated IgM, T & B cell defects, neutropenia.
- **Treatment:** *PjP* prophylaxis, antibiotics, granulocyte colony-stimulating factor for neutropenia. immunosuppressive regimens for autoimmune manifestations. Hematopoietic cell transplantation could provide a curative option.
- **AID/UNG Deficiency:** Less common form of Hyper IgM. Characterized by recurrent sinopulmonary infections, mostly due to encapsulated bacteria, lymphoid hyperplasia, tonsillar hypertrophy, autoimmunity and malignancy

*AID: Activation-Induced Cytidine Deaminase; ^UNG: uracil-DNA glycosylase;

Normal switched memory B cell



Courtesy of Dr. Sara Nandiwada PhD, Clinical Immunology Laboratory, Texas Children's Hospital, Houston,Texas,USA

Selective IgM Deficiency

- **Definition:** Absent/very low IgM and normal IgG/IgA.
- Associated with Autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, Crohn's disease, celiac disease, polymyositis, and Hashimoto's thyroiditis.
- **Symptoms**: Sinopulmonary infections, most commonly seen in children. Adults present with allergies and autoimmunity in addition to these infections.
- **Laboratory**: Low or absent IgM and normal IgA, IgG, normal or impaired response to vaccines. Ruling out other conditions causing low IgM.
- **Treatment:** No commercially available highly enriched IgM preparation. Treatment with IgGRT maybe considered in those with selective antibody deficiency and recurrent infections.

Laboratory evaluation of Humoral Immune Deficiency

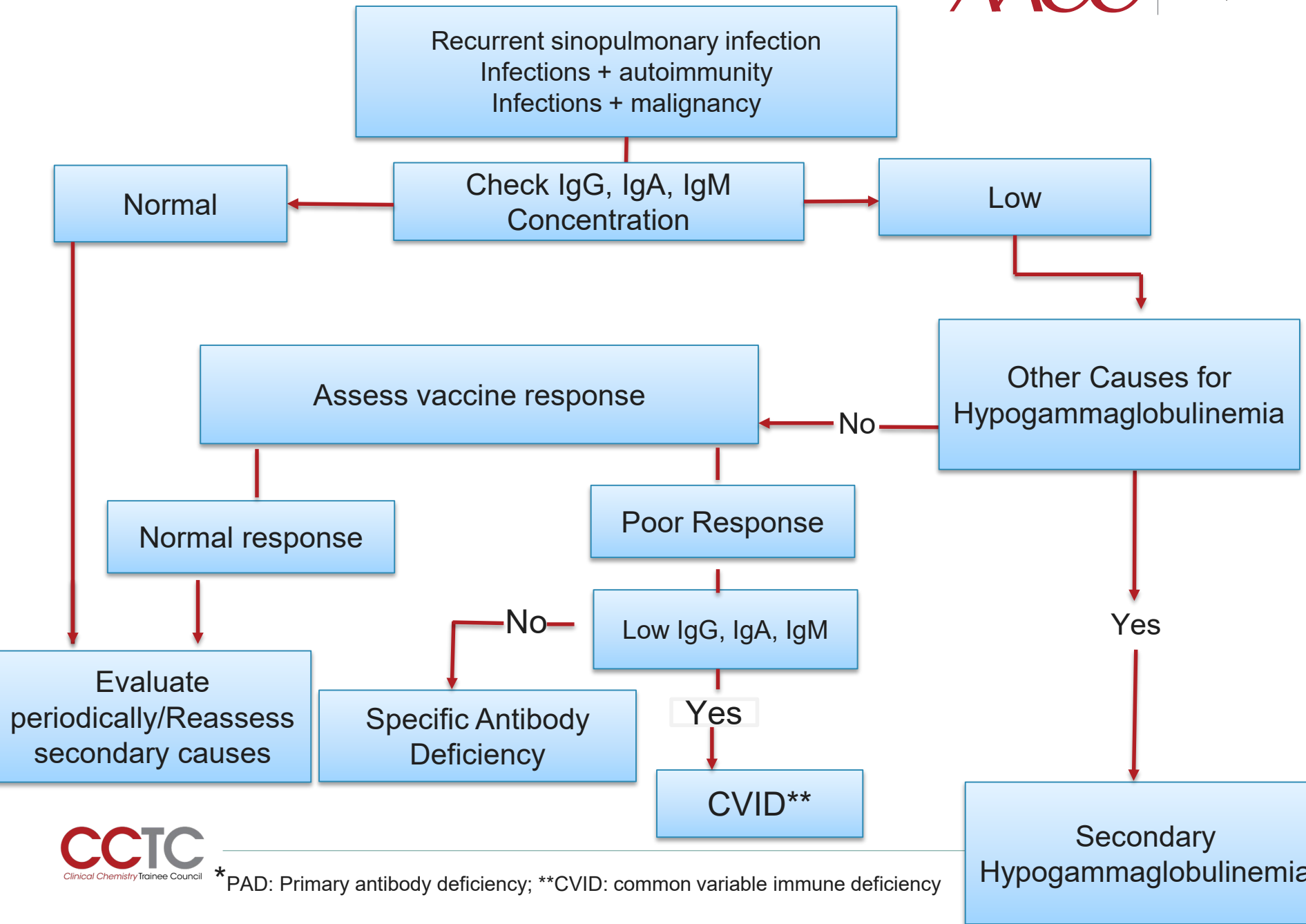
- Targeted History & Physical exam for recurrent infections and autoimmunity
- Quantitative serum Ig (age and sex matched controls)
- Measurement of Antibody production
  - Polysaccharide vaccine, PneumoVax®
  - Protein based: Tetanus, Diphtheria
  - 4 week post-immunization level within protective range, cut off varies with each vaccine. (See Orange et al. 2012)
- Peripheral blood lymphocyte subset analysis

Selected CD markers used in PAD diagnosis

T-cells	CD3
CD4	CD4 ($CD3^+CD4^+$)
CD8	CD8 ($CD3^+CD8^+$)
B-Cells	CD19 ($CD3^-CD19^+$)
Memory B-cell	$CD19^+CD27^+$
Non-switched memory B-cells	$CD19^+CD27^{+l}gM^+IgD^+$
Switched memory B-cells	$CD19^+CD27^{+l}gM^-IgD^-$
Transitional B cells	$CD19^+CD38^{+bright}$
Activated/autoimmune B cells	$CD19^+CD38^{-/low}CD21^{-/low}$

Courtesy of Dr. Sara Nandiwada PhD, Clinical Immunology Laboratory, Texas Children's Hospital, Houston,Texas,USA

Figure 1. Evaluation of PAD*



*PAD: Primary antibody deficiency; **CVID: common variable immune deficiency

References

1. Immune Deficiency Foundation website: http://www.primaryimmune.org/
2. https:Uptodate.com
3. Orange JS, Hossny EM, Weiler CR et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol. 2006 Apr;117(4 Suppl):S525-53.
4. Bonilla FA, Khan DA, Ballas ZK, Chinen J. Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol. 2005 May;94(5 Suppl 1):S1-63.
5. Driessen G , van der Burg M. Educational paper: primary antibody deficiencies. Eur J Pediatr 170: 693-702, 2011.
6. Conley ME, Dobbs AK, Farmer DM et al. Primary B cell immunodeficiencies: comparisons and contrasts Annu Rev Immunol 27: 199–227, 2009.
7. Cunningham Rundles C. Human B cell defects in perspective. Immunol Res 54: 227-32, 2012.
8. Abraham RS. Relevance of antibody testing in patients with recurrent infections. J Allergy Clin Immunol 130: 558-9, 2012.
9. Wood P. Primary antibody deficiency syndromes. Ann Clin Biochem. 2009 Mar;46(Pt 2):99-108. Epub 2009 Jan 16
10. Uygungil B, Bonilla F, Lederman H. Evaluation of a patient with hyper-IgM syndrome. J Allergy Clin Immunol 129:1692-3, 2012.
11. Yong PF, Thaventhiran JE, Grimbacher B A rose is a rose is a rose," but CVID is Not CVID common variable immune deficiency (CVID), what do we know in 2011 Adv Immunol 111:47-107, 2011.
12. Yel L, Selective IgA deficiency. J Clin Immunol 30:10-6, 2010.
13. Krishnaswamy G. Selective IgM deficiency. UpToDate. Waltham, MA: UpToDate; July 26, 2017; http://www.uptodate.com/contents/selective-igm-deficiency.
14. Fried AJ, Bonilla FA. Pathogenesis, diagnosis, and management of primary antibody deficiencies and infections.Clin Microbiol Rev. 2009 Jul;22(3):396-414.
15. Cherry J , Demmler-Hariison GJ, Kaplan SL, Steinbach WJ, Feigin and Cherry's textbook of pediatric infectious diseases. Seventh Edition. 2009.
16. Louis, A.G. Gupta, S. Primary selective IgM deficiency: an ignored immunodeficiency.Clinic Rev Allerg Immunol (2014) 46: 104. https://doi.org/10.1007/s12016-013-8375-x
17. Orange JS1, Ballow M, Stiehm ER et al Use and interpretation of diagnostic vaccination in primary immunodeficiency: a working group report of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol. 2012 Sep;130(3 Suppl):S1-24. doi: 10.1016/j.jaci.2012.07.002
18. Ameratunga R, Brewerton M, Slade C, et al Comparison of Diagnostic Criteria for Common Variable Immunodeficiency Disorder, Front Immunol. 2014; 5: 415.
19. Bonilla FA, Barlan I, Chapel H, et al, International Consensus Document (ICON): Common Variable Immunodeficiency Disorders, J Allergy Clin Immunol Pract. 2016 Jan-Feb; 4(1): 38–59.

Disclosures/Potential Conflicts of Interest

Upon Pearl submission, the presenter completed the Clinical Chemistry disclosure form. Disclosures and/or potential conflicts of interest:

- **Employment or Leadership**: No disclosures
- **Consultant or Advisory Role:** No disclosures
- **Stock Ownership:** No disclosures
- **Honoraria:** No disclosures
- **Research Funding:** No disclosures
- **Expert Testimony:** No disclosures
- **Patents:** No disclosures

Thank you for participating in this *Clinical Chemistry* Trainee Council Pearl of Laboratory Medicine.

Find our upcoming Pearls and other Trainee Council information at www.traineecouncil.org

Download the free *Clinical Chemistry* app on iTunes today for additional content!

Follow us: